

Remarks / Arguments

Claims 1-5, 7-11, 13-17, and 19-25 are pending in the application. Claims 6, 12, and 18 have been cancelled previously. Claims 1-3, 7-9, and 13-15 have been amended in this response.

Comment regarding the restriction requirement

In response to the restriction requirement made in the official action dated 10/10/01, applicants elected to proceed with prosecution of restriction group II. This restriction group related to compounds having the formulae shown in claims 1-3, 7-9, and 13-15 wherein the pyridazine is benzo-fused to form a phthalazine, and wherein the lower ring (shown in claims 1, 7, and 13 as containing A, B, D, E, and L) is a pyridinyl or a diazine ring, plus related pharmaceutical composition and method of use claims.

In response to the applicants' inquiry made in the amendment dated 19 May 2003, the examiner has indicated that the applicants should now remove from the pending claims the non-elected subject matter. This has been done in the present amendment.

Applicants of course reserve the right to file one or more continuing applications to pursue protection for such removed non-elected subject matter.

Comments on the present claim structure and claims

This is a complicated case, with a complicated claim structure. As explained in the summary section of the specification, this invention relates to the sum of three overlapping sets of chemical compounds, which are set forth on pages 4-15 of the specification. These three sets of compounds are the subjects of claims 1, 7, and 13 respectively. Claims 2-3, 8-9, and 14-15 are narrower definitions of the sets of compounds defined broadly by claims 1, 7, and 13 respectively. Thus, it is first necessary to consider claims 1, 7, and 13 in assessing patentability of the claimed compounds.

Claim 1 is intended to distinguish over the art primarily in its definition of the linking group Y of the structural formula, with other groups being defined broadly. Claim 7 is intended to distinguish over the art primarily in its definition of the substituents G³ on the lower heteroaryl

ring of the structural formula, which contains A, B, D, E, and L, with other groups being defined broadly. Claim 13 is intended to distinguish over the art primarily in its definition of the substituents G^4 on the upper ring of the structural formula, with other groups being defined broadly. The preceding statements are not intended to imply that patentability of the claims is to be based only on the groups Y, G^3 , and G^4 , however. It is always necessary to consider the claimed invention as a whole.

The applicants originally intended to require that in claims 7, 8, and 9 the lower heteroaryl ring should be substituted, and that in claims 13, 14, and 15 the upper ring J should be substituted, but through oversight allowed these groups to be unsubstituted. That oversight was corrected in the previous amendment dated 19 May 2003, by deleting the possibility of q being 0 in claims 7, 8, and 9, and deleting the possibility of q' being 0 in claims 13, 14, and 15. Those amendments prevent the present claims from reading on certain prior art compounds.

Rejections under §103

Requirements for a determination of obviousness

In considering the patentability of a claimed invention, the examiner must compare the prior art with the invention as a whole, as claimed. In doing this, the Graham case requires that the examiner consider the scope and content of the prior art, the differences between the prior art and the claimed subject matter, the level of ordinary skill in the art at the time the invention was made, and objective indicia of nonobviousness (if applicable).

For a prima facie obviousness rejection to be valid, the prior art plus general knowledge in the art at the time of the invention must provide a motivation for one skilled in the art to modify the prior art (or combine references) with a reasonable expectation of success, and the references must teach or suggest all the limitations of the claims. The applicant's specification cannot be a basis for motivation, because this would constitute improper "hindsight reconstruction".

Rejection under §103 in view of Bold '812

The examiner has rejected claims 1-5, 7-11, 13-17 and 19-25 under §103 as obvious in view of Bold, for reasons of record. He also provides a restatement of his position in the present official action. Applicants respond as follows.

The examiner has not focused on particular claims in making his rejection, but has operated at a high level of generality. In operating at this high level of generality, the examiner has failed to properly analyze the patentability of the present claims in accordance US requirements, as will be discussed below.

The examiner states, "First of all applicants should note that Bold et al. was applied earlier ad (sic) 102(e) rejection and 103 rejection. Thus the reference anticipates the originally-presented claims and would render them as obvious variant." Applicants respond that the application as previously amended no longer deals with the originally-presented claims, and the examiner is no longer making any rejections on grounds of anticipation. Therefore, the examiner's reference to the original claims as being anticipated and obvious in view of Bold is irrelevant to a consideration of the present claims.

The examiner states, "As for applicants traversal that instant invention is not an obvious variant, based on the applicants own acknowledgement that compounds taught by Bold et al. include compounds of instant invention and that generically claimed compounds of instant invention overlap with those generically taught by Bold et al., clearly negates that argument. Given that fact that Bold et al, exemplifies several compounds and teaches generically compounds that would be useful fro (sic) the utility recited therein, one trained in the art would expect that the genus as whole would have the said utility and would be motivated to make the compounds of the genus given the guidance to make select compounds exemplified therein."

Applicants respond that the examiner appears to have misstated the applicants' position. Applicants have not acknowledged that compounds taught by Bold et al. include compounds of the instant invention and that generically claimed compounds of the instant invention overlap with those generically taught by Bold, as stated by the examiner. On the contrary, applicants believe that the present claims do not claim any compounds of Bold, and that the compounds presently claimed do not overlap with the generic disclosure of Bold. Even if the present generic claims did overlap the generic disclosure of Bold somehow (which the applicants do not

concede), that would not necessarily make the present claims obvious. The issue would then be whether the generic disclosure of the reference somehow suggested the present claims, and that would be arguable. As a general matter, the examiner should be aware that it is quite common for claims of one patent to fall partly or completely within the generic disclosure and claims of another, and this just results in one patent being dominant over the other. Next, the examiner's last sentence quoted above makes no sense: one skilled in the art would be motivated to make compounds within the generic disclosure of Bold only if that generic disclosure and specific examples somehow suggested that those particular compounds within the generic disclosure should be made. The mere fact that a generic disclosure covers a myriad of compounds does not mean that all of those compounds are either disclosed or suggested.

The examiner states, "Contrary to the applicants urging that one need to choose several groups to arrive at the instant compounds, it is held that the compounds taught by Bold et al. would provide adequate guidance to arrive at the compounds generically claimed in Bold and hence the compound of the instant claims would be obvious variant of the teachings of Bold et al." Applicants respond that it is questionable whether the compounds taught by Bold would provide adequate guidance to arrive at the compounds generically claimed in Bold as stated by the examiner, and even if true, this is irrelevant to the question whether the compounds of Bold make the present claims obvious. Applicants stand by their argument (repeated below) that in order to arrive at the presently-claimed compounds certain selections and modifications of the teachings of Bold are required, and these are not suggested by the reference.

The examiner states, "As for applicants' urging that all compounds taught by Bold et al. does not have same IC 50, it is deemed as not a proper comparison to show unexpected/superior results. Applicants should choose the closest prior art compound and compare it with instant compound. Furthermore, applicants have not shown that the all the compounds generically embraced in the instant invention would have the same IC50." Applicants respond that the examiner has again mischaracterized the applicants' argument. In their argument (to be restated below), applicants have not attempted to argue that the presently-claimed compounds exhibit unexpected or superior results, but have argued that Bold teaches away from the compounds of present claim 7, in which the lower ring is required to be substituted. Secondly, contrary to the

examiner's assertion, if comparative testing were to be carried out, it is the examiner's responsibility (not the applicants') to identify what he considers the closest prior art compound, against which the applicants should test. In any event, secondary considerations of non-obviousness only come into play when the examiner has made out a proper prima facie case of obviousness, which the examiner has not done in the present case. Finally, it is not necessary for the applicants to show that all the compounds generically embraced in the present invention have the same IC 50. The issue is not whether the presently claimed compounds have the same IC 50, but whether they have been suggested by the reference. The applicants maintain that no such suggestion has been shown.

Regarding the rejection of the method of use claims, the examiner states, "As for method of use claims 20-25, the rejection is proper as the teaching of Bold et al. relates proliferative diseases. Several diseases recited in these claims appear to proliferative in nature. For example, diabetic retinopathy is a proliferative disease. Applicants can provide evidence the said diseases are not proliferative and therefore not read on the utility taught by the reference." Applicants respond that whether Bold teaches use of his compounds in the treatment of proliferative diseases or not is immaterial to a consideration of the patentability of the present method of use claims. It is the use of the presently-claimed compounds in treatment which is in issue. The method of use claims should be patentable once the presently-claimed compounds are determined to be patentable.

The examiner states, "In response to applicants' argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgement on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971)." Applicants respond that the above-quoted language is a quote from the cited decision, which related to a question whether a combination of certain references was proper as a basis for a rejection for obviousness of claims to railroad boxcars. The court stated "The test for combining references is not what the

individual references themselves suggest but rather what the combination of disclosures taken as a whole would suggest to one of ordinary skill in the art. Any judgement on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper." In the cited decision, the asserted hindsight reconstruction was the selection of prior art references to be combined in making the obviousness rejection. In the present application, the applicants maintain that the only way for the examiner to determine what aspects of the cited prior art should be modified to arrive at the presently-claimed invention is to glean such knowledge from the applicants' own disclosure. The Bold reference does not provide prior art elements which can be added to some second reference to produce the presently-claimed invention (as was the situation in the cited decision), and it does not identify which aspects of its disclosure should be modified in a way pointing to the present claims. To the extent the examiner needs to rely on the present claims to determine how the cited reference disclosure must be modified to arrive at the present claims, this is hindsight reconstruction.

The examiner states, "In the instant case, the compounds of instant claims as noted above are anticipated by Bold et al. and the genus of the instant claims also overlaps with the generically taught genus of Bold et al. Bold et al. clearly teaches equivalency of the compounds exemplified with those generically claimed for the utility taught therein. There is no hindsight analysis is required to make any of the compound of the genus taught by Bold et al." Applicants respond that the presently-claimed compounds are deemed not to be anticipated by Bold, and the genus of the present claims is deemed not to overlap with the generic disclosure of Bold (and even if it did, this should not be determinative) as discussed above. That the presently-claimed compounds and the compounds of Bold are asserted for the same utilities is not material. The hindsight reconstruction question has been discussed above.

Applicants' detailed arguments regarding the Bold '812 reference

In order to arrive at compounds within present claim 1 starting from the Bold '812 disclosure, one must:

- select G to be a lower alkylene substituted with a group selected from the list of G² moieties in the present claim 1 instead of being substituted with the acyloxy or hydroxy substituents disclosed by the reference; or
- select G to be -CH₂-O- but reverse its orientation from that which is shown and required by the teaching of the reference; or
- select G to be -CH₂-S- or -S- but oxidize the S atom to a sulfoxide or sulfone instead of leaving it unoxidized as taught in the reference.

In order to arrive at compounds within present claim 7 starting from the Bold '812 disclosure, one must:

- select as substituent Q of Bold a group selected from the list of G³ substituents shown in the present claim 7, rather than employing a lower alkyl group as taught by the reference.

In order to arrive at compounds within present claim 13 starting from the Bold '812 disclosure, one must:

- select as a substituent on Bold's group Y a group selected from the list of G⁴ substituents shown in the present claim 13, rather than employing any of the many possible substituents shown in the Bold disclosure on col. 5, line 55, through col. 6, line 33.

To arrive at presently claimed compounds starting from the generic disclosure of the '812 reference requires selecting certain moieties from the reference's disclosure and then modifying them in accordance with the requirements of the present claims. The art does not suggest making any of the above-identified modifications to the teachings of the '812 reference, in preference to any of the myriad other possible modifications which could be envisaged in view of the complexity of the subject molecules. Accordingly, it is deemed that the examiner either has not made the required comparison of the presently claimed subject matter and the art, or to the extent he has compared the claimed subject matter and the art, he has employed "hindsight

reconstruction” in reaching his conclusion of obviousness, and that the presently-claimed invention is not obvious in view of the teachings of the ‘812 reference. The fact that the reference teaches variously substituted phthalazines having a certain sort of activity does not suffice to make other variously substituted phthalazines obvious without some suggestion to modify the reference compounds to produce the presently claimed compounds. That suggestion is missing here.

In addition, Bold ‘812 indicates at col. 11, line 52, and at col. 13, line 25, that the subscript “r”, indicating the number of substituents on the lower ring of the structural formula, should preferably be 0. Supporting this preference for having no substituents on the lower ring is Bold’s data on columns 81 and 82, wherein IC₅₀ values are shown for certain of the Bold compounds. Examples 1-4 (which are different salt forms of a compound having no substituents on the lower ring of the structural formula) are shown as having IC₅₀ values between 0.1 and 0.26. Example 44F (which is basically the same compound, but with the lower ring bearing a methyl substituent) is shown as having an IC₅₀ value of 0.624. Thus, Bold’s data indicates that the desired activity decreases by a factor in the range of about 2 – 6 fold when the lower ring bears a substituent. This teaches away from the present claim 7, in which a substituent on the lower ring is required.

Rejection under §103 in view of Watanabe ‘936

The examiner has rejected claims 1-5, 7-11, 13-17 and 19-25 under §103 as obvious in view of Watanabe for reasons of record. Applicants respond as follows.

The examiner states, “As noted in the previous office action, Watanabe et al. clearly generically teaches several compounds which are also claimed in the instant invention and Watanabe also provides guidance for making 72 compounds. There is clear teaching of equivalency to the generically claimed compounds with those exemplified in the 72 examples for the utility taught therein. There is enough guidance for one to choose compounds from the genus and there is expectation that such compounds would also share the same utility. Thus the requirement of 103 rejection, motivation and expectation of success is met with.”

Applicants respond that they do not believe that the present claims cover compounds within the generic or specific disclosure of the Watanabe '936 reference, and that the teaching of the reference does not suggest the presently-claimed compounds, contrary to the examiner's assertion.

Regarding the rejection of the method of use claims, again it is argued that these should be patentable once the claims to chemical compounds are determined to be patentable. The mode of action should not be material.

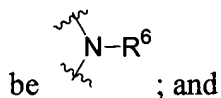
Applicants' detailed arguments regarding the Watanabe '936 reference

As with the rejection in view of Bold, the examiner has not focused on particular claims in making his rejection, but has operated at a high level of generality. In operating at this high level of generality, the examiner has failed to properly analyze the patentability of the present claims in accordance US requirements, as will be discussed below. Applicants stand by their argument (repeated below) that in order to arrive at the presently-claimed compounds certain selections and modifications of the teachings of Watanabe are required, and these are not suggested by the reference.

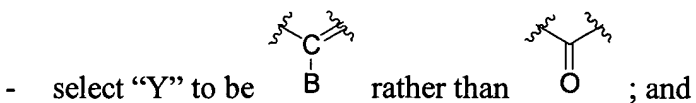
In order to arrive at compounds within present claim 1 starting from the '936 disclosure, one must:

- select "A" to be $-NR^4R^5$, rather than H, a halogen atom, an optionally substituted aryl group, an optionally substituted heteroaryl group, an optionally substituted arylalkyl group, or an optionally substituted heteroarylalkyl group; and
- select one of R^4 and R^5 to be an optionally substituted arylalkyl group (in particular, a phenylalkyl group) or an optionally substituted heteroarylalkyl group (in particular, a pyridylalkyl group), rather than allowing R^4 and R^5 each to be H, an optionally substituted lower alkyl group, an acyl group, or allowing R^4 and R^5 to be joined to form a heterocyclic group; and

- select "X" to be a N atom which is doubly bonded in an aromatic ring (i.e., the bond shown as "====" is a double bond rather than a single bond), rather than allowing X to



- select ring "C" as a 6-membered ring, rather than a 5-membered ring; and

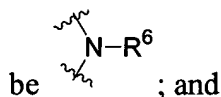


- select "B" to be an SR¹³ group or an optionally substituted heteroarylalkyl group, rather than allowing B to be H, a halogen atom, an -NR⁷R⁸ group, an -OR¹² group, an optionally substituted aryl group, an optionally substituted heteroaryl group, or an optionally substituted arylalkyl group; and
- when "B" is an SR¹³ group, select the R¹³ moiety to be an optionally substituted heteroarylalkyl group, rather than H, an optionally substituted lower alkyl group, an acyl group, or an optionally substituted arylalkyl group, and oxidize the S atom to a sulfoxide or a sulfone; and
- when "B" or R¹³ is an optionally substituted heteroarylalkyl group, select as the heteroaryl portion a 6-membered monocyclic heteroaryl group containing at least one N atom, rather than a 5-membered or polycyclic heteroaryl group or a heteroaryl group containing no N atoms; and
- when "B" is an optionally substituted heteroarylalkyl group, select a cyano, ester, or amide substituent, rather than a hydroxyl, nitro, amino, acyl, lower alkoxy, or halogen; and select the location for one such substituent as the alkyl portion of the heteroarylalkyl group, rather than the heteroaryl portion.

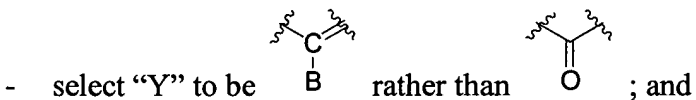
In order to arrive at compounds within present claim 7 starting from the '936 disclosure, one must:

- select "A" to be -NR⁴R⁵, rather than H, a halogen atom, an optionally substituted aryl group, an optionally substituted heteroaryl group, an optionally substituted arylalkyl group, or an optionally substituted heteroarylalkyl group; and

- select one of R^4 and R^5 to be an optionally substituted arylalkyl group (in particular, a phenylalkyl group) or an optionally substituted heteroarylalkyl group (in particular, a pyridylalkyl group), rather than allowing R^4 and R^5 each to be H, an optionally substituted lower alkyl group, an acyl group, or allowing R^4 and R^5 to be joined to form a heterocyclic group; and
- select "X" to be a N atom which is doubly bonded in an aromatic ring (i.e., the bond shown as " ---- " is a double bond rather than a single bond), rather than allowing X to



- select ring "C" as a 6-membered ring, rather than a 5-membered ring;



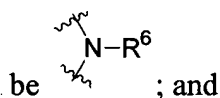
- select "B" to be -NR⁷R⁸ or -OR¹² or SR¹³ or a manditorily substituted heteroarylalkyl group, rather than allowing B to be H, a halogen atom, an optionally substituted aryl group, an optionally substituted heteroaryl group, or an optionally substituted arylalkyl group; and

- when "B" is -NR⁷R⁸, select one of R^7 and R^8 to be a manditorily substituted heteroarylalkyl group, rather than allowing R^7 and R^8 each to be H, an optionally substituted lower alkyl group, an acyl group, an optionally substituted arylalkyl group, or allowing R^7 and R^8 to be joined together to form a heterocycle; and
- when "B" is -OR¹² or -SR¹³, select R^{12} or R^{13} to be a manditorily substituted heteroarylalkyl group, rather than allowing it to be H, an optionally substituted lower alkyl group, an acyl group, or an optionally substituted arylalkyl group; and
- when R^7 , R^8 , R^{12} or R^{13} is a manditorily substituted heteroarylalkyl group, select as the heteroaryl portion a 6-membered monocyclic heteroaryl group containing at least one N atom, rather than a 5-membered or polycyclic heteroaryl group or a heteroaryl group containing no N atoms; and

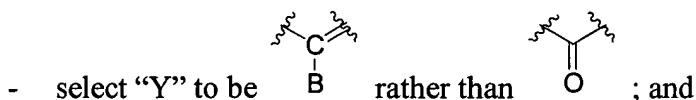
- when "B", R^7 , R^8 , R^{12} , or R^{13} is a manditorily substituted heteroarylalkyl group, require at least one substituent selected from the group defined as G^3 in present claim 7 to be located on the heteroaryl portion.

In order to arrive at compounds within present claim 13 starting from the '936 disclosure, one must:

- select "A" to be $-NR^4R^5$, rather than H, a halogen atom, an optionally substituted aryl group, an optionally substituted heteroaryl group, an optionally substituted arylalkyl group, or an optionally substituted heteroarylalkyl group; and
 - select one of R^4 and R^5 to be a manditorily substituted arylalkyl group (for example, a phenylalkyl group) or a manditorily substituted heteroarylalkyl group (in particular, a pyridylalkyl group), rather than allowing R^4 and R^5 each to be H, an optionally substituted lower alkyl group, an acyl group, or allowing R^4 and R^5 to be joined to form a heterocyclic group; and
 - when R^4 or R^5 is a manditorily substituted arylalkyl or pyridylalkyl group, require at least one substituent selected from the group defined as G^4 in present claim 13 to be located on the phenyl or pyridyl portion, rather than employing any of the possible substituents listed on page 4, lines 12-15 of the reference (note that Watanabe's list of possible substituents does not overlap with the list of G^4 substituents shown in present claim 13); and
- select "X" to be a N atom which is doubly bonded in an aromatic ring (i.e., the bond shown as "====" is a double bond rather than a single bond), rather than allowing X to



- select ring "C" as a 6-membered ring, rather than a 5-membered ring; and



- select "B" to be $-NR^7R^8$ or $-OR^{12}$ or SR^{13} or an optionally substituted heteroarylalkyl group, rather than allowing "B" to be H, a halogen atom, an optionally substituted aryl

group, an optionally substituted heteroaryl group, or an optionally substituted arylalkyl group; and

- when “B” is $-NR^7R^8$, select one of R^7 and R^8 to be an optionally substituted heteroarylalkyl group, rather than allowing R^7 and R^8 each to be H, an optionally substituted lower alkyl group, an acyl group, an optionally substituted arylalkyl group, or allowing R^7 and R^8 to be joined together to form a heterocycle; and
- when “B” is $-OR^{12}$ or $-SR^{13}$, select R^{12} or R^{13} to be an optionally substituted heteroarylalkyl group, rather than allowing it to be H, an optionally substituted lower alkyl group, an acyl group, or an optionally substituted arylalkyl group; and
- when R^7 , R^8 , R^{12} or R^{13} is an optionally substituted heteroarylalkyl group, select as the heteroaryl portion a 6-membered monocyclic heteroaryl group containing at least one N atom, rather than a 5-membered or polycyclic heteroaryl group or a heteroaryl group containing no N atoms.

The applicants maintain that in making his rejection of the claims in view of the Watanabe '936 reference, the examiner has failed to make the required comparison of the differences between the prior art and the invention as presently claimed and has failed to show a suggestion in the art sufficient to motivate one to select from the teachings of the prior art those particular definitions of variables which will generate compounds within the present claims, or to the extent he has compared the presently claimed subject matter with the art, he has used impermissible “hindsight reconstruction” in view of the applicants’ own disclosure to reach his conclusion of obviousness. The discussion above relating to the many selections of variables which must be made in the generic teachings of the reference in order to derive any presently-claimed compounds, plus the lack of any suggestion in the art that the particular sets of required selections should be made, makes it clear that either the examiner did not make the requisite comparison, or that the applicants’ own specification was the basis for the examiner’s conclusion of obviousness. Without the present specification as a guide to the goal, there would be no way for the examiner to decide which selections of variables from the generic disclosure of the reference should be made in order to arrive at compounds within the present claims.

Accordingly, it is deemed that the rejection for obviousness in view of the '936 reference is flawed and its withdrawal is requested.

Objection to claim 19

Claim 19 was objected to as being dependent upon a rejected base claim, but the examiner states that this claim would be allowable if rewritten in independent form. The examiner should note that claim 19 is already in independent form. It should therefore be allowable.

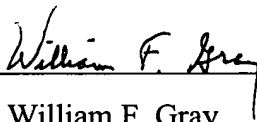
In view of the above amendments and arguments, this application is deemed to be in condition for allowance, and allowance is accordingly requested.

Respectfully submitted,

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Date: 13 July 2004



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